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EXAMINER	
BAUSCH, SARAE L	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,180	SAWITZKI ET AL.	
	Examiner	Art Unit	
	Sarae Bausch PhD	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-58* is/are pending in the application.

4a) Of the above claim(s) *26-39, 47, 49-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-46,48 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 26-58 are pending in the instant application. Claim 1-25 have been canceled. Claims 26-39, 47, 49-57 are withdrawn and claim 58 is newly added. This action is written in response to applicant's correspondence submitted 06/05/2009. All the amendments and arguments have been thoroughly reviewed but were found insufficient to place the instantly examined claims in condition for allowance. The following rejections are either newly presented, as necessitated by amendment, or are reiterated from the previous office action. Any rejections not reiterated in this action have been withdrawn as necessitated by applicant's amendments to the claims. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is Final.**

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 40-46, 48, and 58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is newly presented as necessitated by the amendment to the claims.

Claim 40 and 58 recite "wherein SEQ ID NO 7 is at least one nucleic acid molecule selected from the group consisting of....and combinations thereof" which renders the claim indefinite. This recitation is defining SEQ ID NO 7 as any of the nucleic acid molecules in a-e of the claims, which encompasses any nucleic acid (as (a) recites a nucleic acid molecule); any

nucleic acid sequence that has been modified by deletions, additions, substitutions, translocations, inversions, and or insertions; or any nucleic acid molecule that exhibits a genetic code degeneration relationship. The claim is indefinite as it appears that the claim is requiring that SEQ ID NO 7 is not the sequence set forth in the sequence listing but that SEQ ID NO 7 is some other sequence that is not defined in the specification but described in the claims as any sequence or any sequence with any modification. It appears that applicant is specifically defining a term, SEQ ID NO 7, contrary to its meaning which is the sequence associated with identifier 7 as set forth in the instant specification. By applicant redefining SEQ ID NO 7 in the claim and the specification not clearly redefining the term renders the claim indefinite.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 40-46, 48, and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is newly presented necessitated by the amendment to the claims. This rejection is a new matter rejection.

Claim 40 and 58 recite "wherein SEQ ID NO 7 is at least one nucleic acid molecule selected from the group consisting of....and combinations thereof". This recitation is not supported in the specification and raises the issue of matter. This recitation broadens the

definition of SEQ ID NO 7 and thus broadens the scope of the claims, which is not support in the instant specification. The specification defines SEQ ID NO 7 as the sequence set forth in the sequence listing and is T8 a rat cDNA, see figure 1C. The specification does not however teach that SEQ ID NO 7 is any nucleic acid sequence as recited in the claims or any nucleic acid with any homologue, insertion, deletion, inversion, translocation. The claims recite wherein SEQ ID NO 7 is at least one nucleic acid molecule selected from the group consisting of a nucleic acid molecule and therefore the claims are defining SEQ ID NO 7 as any nucleic acid sequence. The specification does have literal for support for a nucleic acid molecule of SEQ ID NO 7, a nucleic that will hybridize to SEQ ID NO 7, a nucleic acid that exhibits genetic code degeneration relationship with respect to SEQ ID NO 7, and nucleic acid that has been modified by deletions, additions, substitutions, translocation, inversions and/or insertions of SEQ ID NO 7 but does not have support for wherein SEQ ID NO 7 is at least one nucleic acid molecule that is a nucleic acid molecule nor nucleic acid molecules that have genetic code degeneration relationship to any sequence or modification of any sequence as recited in the amendment to the claims.

6. Claims 40-46, 48, and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is newly presented necessitated by the amendment to the claims and is a written description rejection.

> Applicant is referred to the revised training materials on written description available at www.uspto.gov/web/menu/written.pdf. Of particular relevance to the rejected claims 40-46, 48, and 58 are examples 7 and 17 on page 25-28 and 58-60

of the training materials addressing methods of graft reaction claimed by functional limitations.

The rejected claims are broadly drawn to methods for a detecting graft reaction in a subject and in a human by determining a level of SEQ ID NO 7 in the sample and comparing to a control level, wherein SEQ ID NO 7 is at least one nucleic acid molecule selected from the group consisting of a nucleic acid molecule, a nucleic acid molecule that hybridizes to SEQ ID NO 7, a nucleic acid molecule that has sufficient homology to a nucleic acid molecule or nucleic acid molecule that hybridizes to SEQ ID NO 7, a nucleic acid molecule that exhibits a genetic code degeneration relationship with respect to a nucleic acid molecule or a nucleic acid molecule that hybridizes to SEQ ID NO 7, and a nucleic acid molecule that has been modified by deletions, additions, substitutions, translocation, inversions, and/or insertions and a functional analogues of a nucleic acid sequence or a nucleic acid sequence that hybridizes to SEQ ID NO 7.

When the claims are analyzed in light of the specification, the instant invention encompasses methods comprising the analysis and detection of an enormous and wide variety of nucleic acid sequences. The claims are broadly drawn to a method that encompass a plurality of nucleic acids of an extremely large genus of any nucleic acid sequence, its homologue and modifications of deletions, additions, substitutions, translocations, inversions and insertions as well as any sequence that hybridizes to SEQ ID NO 7 with any nucleotide content (A or G or C or T) at any position within a nucleic acid sequence or nucleic acid sequence that hybridizes to SEQ ID NO 7 in any subject as well as human. Thus the claims encompass the detection of any of the many different nucleic acids wherein the nucleic acid sequence is correlated with a graft reaction. Nucleic acids of such a large genus have not been taught by the specification.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. The instant specification provides the sequence of SEQ ID No. 7 which is the rat cDNA sequence of the T8 gene. The specification does not provide any homology, functional analogue, genetic code degeneration relationship, or modifications of SEQ ID NO 7 much less to any nucleic acid sequence nor provide any of these sequence and their association with graft reactions.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e. other than nucleotide sequence, gene name, and specific polymorphic position), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the specification provides only the sequence of SEQ ID no. 7, which is a rat cDNA and the specification does not provide the human homologue or any modification of SEQ ID NO 7 in any other species. The specification does not provide any characteristics that would allow one to identify any particular portions or fragments or variants of the disclosed sequence that would allow for the detection of graft reaction based on detection of the non-disclosed gene. Neither the specification nor the prior art teach an association SEQ ID NO 7 or any homologue or modification of SEQ ID NO 7 with a graft reaction.

Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A. (Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems

> evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, or perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In the instant application, because of the lack of any analysis regarding homologues and modifications of SEQ ID NO 7 or any nucleic acid sequence, as broadly claimed, one of skill in the art cannot envision the detailed chemical structure of the nucleic acid encompassed by the claimed methods, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that such nucleic acids are part of the invention and reference to a potential method for identification. The particular nucleic acids are themselves required.

In conclusion, the limited information provided regarding the nucleic acids of the claimed methods is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a method for determining graft reaction in a subject, both human and non-human by detecting the determining a level of SEQ ID NO 7 in the sample and comparing to a control level, wherein SEQ ID NO 7 is at least one nucleic acid molecule selected from the group consisting of a nucleic acid molecule, a nucleic acid molecule that hybridizes to SEQ ID NO 7, a nucleic acid molecule that has sufficient homology to a nucleic acid molecule or nucleic acid molecule that hybridizes to SEQ ID NO 7, a nucleic acid molecule that exhibits a genetic code degeneration relationship with respect to a nucleic acid molecule or a nucleic acid molecule that hybridizes to SEQ ID NO 7, and a nucleic acid molecule that has been modified by deletions, additions, substitutions, translocation, inversions, and/or insertions and a functional analogues of a nucleic acid sequence or a nucleic acid sequence that hybridizes to SEQ ID NO 7.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

7. Claims 40-46, 48, and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection was previously presented and has been rewritten to address the amendment to the claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are a method for determining graft reaction in a subject, both human and non-human by detecting the determining a level of SEQ ID NO 7 in the sample and comparing to a control level, wherein SEQ ID NO 7 is at least one nucleic acid molecule selected from the group consisting of a nucleic acid molecule, a nucleic acid molecule that hybridizes to SEQ ID NO 7, a nucleic acid molecule that has sufficient homology to a nucleic acid molecule or nucleic acid

molecule that hybridizes to SEQ ID NO 7, a nucleic acid molecule that exhibits a genetic code degeneration relationship with respect to a nucleic acid molecule or a nucleic acid molecule that hybridizes to SEQ ID NO 7, and a nucleic acid molecule that has been modified by deletions, additions, substitutions, translocation, inversions, and/or insertions and a functional analogues of a nucleic acid sequence or a nucleic acid sequence that hybridizes to SEQ ID NO 7. Additional claims are drawn to graft that is lung, spleen, heart, kidney, liver, pancreas, or tissue (claim 41) or islets, aortas, cartilage (claim 42), as well as level is determined by gene expression, number of copies of nucleic acid, DNA or RNA concentration (claim 43) or mRNA concentration (claim 44). The claims are further limited to rejection crisis, rejection reaction, course of rejection, tolerance reaction, or course of tolerance (claim 45) and is detected by reduced level (claim 46) or increased level (claim 48)of nucleic acid molecule. Claim 58 is drawn to a method for detection of graft reaction in a sample from a patient by characterizing the level of SEQ ID No 7 in a sample compared to a control level of a comparative sample from a healthy patient wherein the graft reaction or absence thereof is detected by a modified level in the sample compared to control in a human.

The rejected claims (claims 40-44 and 46) encompass analysis of any patient, human and non-human. Claims 40-44 encompass any type of graft reaction, including any type of rejection and tolerance and any increase or decrease level of SEQ ID NO 7 detection. Claims 40, 43-46 and 48 encompass any type of graft.

The rejected claims encompass analysis of any nucleic acid sequence, any nucleic acid molecule that has sufficient homology to a nucleic acid molecule or nucleic acid molecule that hybridizes to SEQ ID NO 7, any nucleic acid molecule that exhibits a genetic code degeneration

relationship with respect to a nucleic acid molecule or a nucleic acid molecule that hybridizes to SEQ ID NO 7, and a nucleic acid molecule that has been modified by deletions, additions, substitutions, translocation, inversions, and/or insertions and a functional analogues of a nucleic acid sequence or a nucleic acid sequence that hybridizes to SEQ ID NO 7

The nature of the claims requires the knowledge of a correlation between the detection level of SEQ ID No 7, any modification, any homologue of any nucleic acid sequence and a graft reaction. Thus the claims require the knowledge that the rat cDNA sequence will detect graft reaction in a human (claim 58) as well as any homologue or variant of SEQ ID NO 7 will be correlated to graft reaction in any subject, human or non-human.

The invention is in a class of inventions which the CAFC has characterized as "the unpredictably arts such as chemistry and biology" (Mycolgen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Guidance in the Specification

The specification asserts that the invention provides efficient and reliable immune markers which enable a certain and fact prediction of risk of graft rejection or the absence thereof, as a form of tolerance (see pg. 4 lines 22-26). The specification assert that rejections are defined by functional deterioration of organs, however the specification teaches that functional deterioration is not always due to rejection but can be caused by toxicity and infection (see pg. 2 lines 25-30). The specification asserts that detection of graft reaction in a sample from a patient is determined in a sample by a level of a nucleic acid and the level is compared with a control level of a comparative sample from a healthy patient, wherein the graft reaction are detected by a modified level in the sample compared to control level (see pg. 9 lines 5-8). The specification

does not provide any guidance on if an increase or decrease level of nucleic acid is predictive of graft reaction in a patient. For example, the specification does not indicate or provide any guidance that an increase or decrease , and how much increase or decrease of SEQ ID NO 7 would be predictive of a rejection or tolerance of a graft in a human or any other organism. The specification does not teach analysis of SEQ ID NO 7 in a human nor teach that expression of SEQ ID NO 7 would be capable of being detected in human to then determine graft reaction. The specification does not teach analysis of any modification or functional analogue SEQ ID NO 7 and its correlation to graft reaction.

The specification further asserts that graft reaction means any physiological and pathophysiological interaction of the graft with the receptor organism, but also any isolated reaction within the graft. The specification teaches that the graft reaction can be tolerance or a rejection of the graft (see pg. 9 lines 9-30). The specification further defines a patient as an organism that comprises a graft, especially human organism, thus the claims encompass any human or non-human organism that comprises a graft (see pg. 10 lines 11-12) and asserts that graft comprises lung, spleen, heart, liver, pancreases and tissues, islets, aortas, cartilage (See pg. 10 lines 24-26). The specification asserts that modification means that the nucleic acid molecule exhibit detectable changes in their concentration compared to a control level (see pg. 10 lines 19-23), however the specification does not provide guidance on how much change is required and how this change correlates to graft reaction in any species.

The specification teaches that rejection reaction, course of rejection and rejection crisis is detected by an increased level of nucleic acid (see pg. 12 lines 16-30) and teaches that tolerance and course of tolerance is detected by an increased level of nucleic acid (see pg. 13 lines 13-28).

Thus, based on the guidance in the specification it is unpredictable to determine an increased level of SEQ ID NO 7 to determine graft reaction, as both a tolerance and rejection would be indicated by increased levels of SEQ ID NO. 7. Furthermore, SEQ ID NO 7 is a cDNA from a rat (See pg. 17 ex 1). The specification does not indicate nor provide any guidance that this sequence is also present in other organisms, and even if this sequence was present in other organisms, the specification provides no guidance on how the level of this sequence would be indicative of graft reaction in other species.

The specification provides a working example of isolating mononuclear cells from receptor animals treated with control antibodies and isolated cDNA fragments that were expressed at increased levels in grafts of tolerance-developing receptor animals (see pg 17 last para cont'd to page 18, first para). Figure 2 demonstrates the results of expression analysis for T8 (SEQ ID NO 7) for kidney transplantation model in rats. The specification asserts that all cDNA fragments were strongly expressed in permanently accepted grafts but grafts of receptor animals treated with control antibodies, their expression is decreased at the time of rejection (see pg. 18 lines 21-30). However, figure 2 demonstrates that in the first 10 days expression of SEQ ID NO 7 in both rat models is decreased and after ten days the expression level increases above the lowest expression level but this graph does not indicate that SEQ ID NO 7 is strongly expressed in permanently accepted grafts as both the control and RIB5/2 assayed have decreased expression initially and the expression level in RIB5/2 never exceeds the initial expression level. Thus figure 2 and example 1 does not provide any guidance on how to determine that the expression level of SEQ ID NO 2 is predicative of graft reaction when both the tolerance and rejected models have decreased expression levels.

The specification asserts that figure 3 corresponds to mRNA from heart transplantation model. The specification asserts that mRNA expression is reduced in rejecting receptor animals while the accepted graphs exhibit a high mRNA expression for T8, which is reflected in both the graft and peripheral blood (see pg. 19 lines 1-12). The specification asserts that a strong expression drop of T8 in the periphery in rejecting receptor animals more than 2 days before a clinical manifestation of rejection enables non-invasive diagnostics in the blood (see pg. 20 lines 4-8). However, figure 3 demonstrates that the expression levels of both the rejecting receptor animal and the accepted grafts exhibit the same expression levels (see figure 3, T8). Additionally, the expression level of accepted graft does increase over time however this is not an increase relative to the initial expression level, nor does the graph evaluate the expression level of T8 in the rejecting receptor animal over the entire time period to determine if the increase in expression after 10 days is the same in both models. Additionally, figure 4 demonstrates the expression level in blood and demonstrates that T8 does not increase or decrease in the accepted graft, thus it can not be concluded that an increase level of SEQ ID NO 7 is indicative of accepted graft as neither figure 3 nor figure 4 demonstrate that the expression level of SEQ ID NO 7 increases nor does the specification provide data that is statistically significant to determine that the increase is predictive. Furthermore, the specification does not teach what is encompassed by an accepted graft in the animal models.

The specification provides a working example of mice which accept allogenic livers spontaneously. The specification asserts that figure 7 summarizes the results and that spontaneous tolerance with transient self-limiting rejection crisis is reflected by a high expression of tolerance markers T8. However, figure 7 only demonstrates expression level of a

mouse that accepts allogenic livers spontaneously and demonstrates that the expression level of SEQ ID NO 7 does not change over time for the tolerance, however the figure does not evaluate SEQ ID NO 7 in a control population, such as a rejection group to determine if the expression level is indicative of tolerance.

It is unclear from the lack of guidance in the specification how to determine a graft reaction in any patient by measuring the level of SEQ ID NO 7 to a control sample. The specification only gives limited guidance with respect to working examples of determining expression levels in rat and mouse models of heart, kidney, and liver transplants. The specification does not demonstrate expression levels of SEQ ID NO 7 in any other organ or tissue or in any other patient population other than the rat and mouse models. The specification does not teach any sequences with modification, functional homologues, variations of SEQ ID NO 7 and this sequence association with graft reaction. The specification does not provide guidance on the amount of expression that is predictive of tolerance or rejection of graft. The specification only gives limited guidance with respect to decreases in expression levels in a rat model and a mouse model. Additionally, the specification does not provide any statistical analysis to predictably associate an expression level of SEQ ID NO 7 with graft reaction.

The specification does not teach a predictive value or a connection between the expressed SEQ ID NO 7 and the status of the accepted and rejected grafts. The specification does not provide any guidance with the status of the graft, for example the specification does not evaluate heart function, liver function, or kidney function of the accepted grafts for SEQ ID NO 7 to provide guidance on what constitutes an accepted graph versus a rejected graft. Based on the

teachings in the specification, it is unclear how the expression level of SEQ ID NO 7 would determine graft reaction in any patient.

The specification does not provide any guidance of expression levels of SEQ ID NO 7 of grafts in human nor does the specification teach that expression level of SEQ ID NO 7 in grafts of spleen, pancreas, tissue, inslets, aorta, or cartilage much less the reaction of the graft of each of these organs or tissues in any patient population. The specification does not provide any statistically significant expression level data that would predictably determine that the expression level of SEQ ID NO 7, either an increase or decrease, would be associated with a graft reaction. It is unclear how the skilled artisan would be able to determine a graft reaction in a patient because the specification does not teach the level of SEQ Id NO 7 that is correlative to different graft reactions with different types of grafts in different organisms. The specification only demonstrates expression level of SEQ ID NO 7 in rat model and mouse model of heart and kidney graft, as well as liver graft, however the patient population of this study appears to extremely small, consisting of only one rejected graft animal and one accepted graft animal for kidney and heart grafts and only one accepted graft animal for liver grafts were evaluated.

The specification envisions hypothetical situations where expression level of SEQ ID NO 7, both an increase and decrease could determine both a tolerance and a rejected graft reaction in any patient population. The specification appears to be conceiving of possible scenarios where any expression level of a rat cDNA, SEQ ID NO 7 could be used to determine graft reactions in other species, however it is unclear how one of skill in the art would determine the level of expression necessary to determine if the graft is either rejected or accepted as well as if SEQ ID

NO 7 even exists in other species, much less if SEQ ID NO 7 is then expressed in grafts of other species and predictive of graft reactions in these species.

The unpredictability of the art and the state of the prior art

While the state of the art and level of skill in the art with regard to detection of a gene expression is high, the level of unpredictability in associating any particular expression level with a phenotype is even higher. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

The prior art does not teach any association between SEQ ID NO 7 and graft reaction. The prior art teaches that there are many parameters that are needed to be evaluated prior to using gene expression as a test to determine graft reaction.

It is unpredictable as to whether or not a sequence comprising SEQ ID NO 7 exists in any human or non-human organisms other than rattus novergicus, and whether or not detection of a SEQ ID NO 7 in any other organism would be predictive of graft reaction. For example, Coleman (DDT, 2003, vol. 8 no. 6, pp. 233-235) analyzes direct comparison of gene expression in mice and humans. Coleman teaches that the basic pattern of gene expression between mice and human differs and that 59% of gene are expressed in all tissues but at greatly differing levels (see pg. 234, 2nd column, last para). Coleman teaches mouse and human gene expression patterns and teaches that not all patterns are similar and that the validity of mouse or other animal species as a human surrogate should not be assumed and some attempt should be made to establish its suitability, such as comparative gene expression studies (see pg. 235, last para). Additionally, Seddiqi et al. (J Mol Evol (1994), vol. 39, pp. 655-660) teaches comparison of mRNA expression of a gene among different species of Rattus norvergicus, Bos taurus, and

Homo sapiens. Seddiqi teaches that the coding sequence of protein h3 between R. norvegicus and H. sapien is 88.5% identical and Bos Taurus and Rattus norvergicus is 94% identical (see pg. 1st column, last para), the expression of the mRNA in different tissues among the different species is vastly different (see figure 3a-c). Therefore, Seddiqi et al. teaches that a H. sapiens protein h3, that is very closely related structurally to both B. Taurus and R. norvegicus has great variability of mRNA level and this mRNA level is dependent on both tissue and species (see pg. 660, 1st column, last para). Thus both Seddiqi and Coleman teach that it is not predictable to determine expression level of a nucleic acid among different species and difference tissues and thus its unpredictable to extrapolate that expression level of one nucleic acid to any tissue and any species, based on expression level of SEQ ID NO 7 in rattus norvegicus. Thus it is entirely unpredictable as to whether or not the level of SEQ ID NO 7 would be associated with graft reaction in any tissue in any species.

Shalon et al. (US 2001/0051344 A1 Dec 13, 2001) teach that due to variations in genetic make-up of unrelated individuals in a heterogeneous society, differences in the expression of a gene between any two individuals may or may not be significant (see page 10, paragraph 0155). Shalon et al. further teach that the larger the number of individuals tested, the more significant the remaining differences in gene expression become and samples from at least 5 and preferably 20-50 different test individuals are assayed to obtain statistically meaningful data showing a statistical elevation or reduction in report levels when compared to control levels (see page 10, paragraph 0156). Sharlon et al. teach that the test average pattern is compared with a control average pattern on a microarray to identify test genes which show significantly, typically at least 2 fold and up to 100 fold or more, increase or decrease in gene expression level with respect to

control levels for the same gene (see page 10, paragraph 0158). Post filing art, Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) teach genetic tests are heterogeneous in nature and the exact characteristics of a particular genetic test to be evaluated must be tightly defined. Kroese et al. teach that a particular genetic condition may be caused by more than one gene and these variations may be due to deletions and insertions not detected by routine sequence methods. (see page 476, 2nd column, last paragraph). Kroese et al. teach that genetic test is shorthand to describe a test to detect a particular genetic variant for a particular disease in a particular population and for a particular purpose and that it should not be assumed that once the characteristics of a genetic test are evaluated for one of these reasons that the evaluation will hold or be useful for other purposes and all measures of the test performance should be presented with their 95% confidence intervals (see page 477, 1st column, 1st and 2nd full paragraph). Kroese et al. teach that the limitations of our genetic knowledge and technical abilities means that for the moment there are likely to be gaps in the information needed to complete a thorough evaluation of many genetic tests (see page 479, 2nd column, last paragraph).

Furthermore, Ionnidis (Plost Med, 2005, 2(8):e124) teach that most published research findings are false. Ionnidis et al. teach that ill-founded strategy of claiming conclusive research finding solely on the basis of a single study assed by formal statistical significance represented and summarized by p values (see pg. 0696, 2nd column, 1st full para.) Ionnidis et al. teach that research findings are likely to be true that in fields that undertake large studies, such as randomized controlled trials (several thousand subjects randomized) than in small studies such as sample sizes 100 fold or smaller (see pg. 0697, 3rd column, 2nd full para.) Ionnidis et al. teaches that what matters is the totality of evidence and that statistical significance of a single study only

gives a partial picture (see pg. 0701, 1st column). Additionally, Hattersley et al. (Lancet, 2005, vol 366, pp. 1315-1323) teaches that the key quality in an association study is sample size (see page 1318, 2nd column, 1st full paragraph). Hattersley et al. teach that sample sizes of thousands are needed to detect variants that are common but have low relative risk and teach that allelic odds ratio of 1.1 to 2.0 requires the number of controls to be in thousands (see page 1318, 2nd column, 1st full paragraph and table 3). Hattersley et al. teach that apparent studies in identifying interesting associations with studies much smaller than implied by table 3 (in the thousands) might suggest that calculations are too pessimistic and small initial studies rarely find the correct result and even when they do they are likely to overestimate the true effect size (see page 1318, 1st column, 1st full paragraph). Hattersley et al. further teaches that emphasis has been on the need for greater stringency in the association studies in order to prove a given association and suggest a p value of $5x10^{-8}$, however arguments from Bayesian perspective suggest that $5x10^{-5}$ should be sufficient to constrain the false discovery rate.

Therefore, based on the prior art teachings, coupled with the data presented in the specification it is unpredictable to correlate levels of SEQ ID NO 7 with graft reaction in any patient, as the specification does not teach a large sample size, confidence levels greater than 95%, or analysis of SEQ ID NO 7 in other species.

Quantity of Experimentation

Given the lack of guidance in the specification with regard to association of the level SEQ ID NO 7 with a graft reaction in "any" species the quantity of experimentation in this area is extremely large. The skilled artisan would have to perform an extremely large study and include different species populations and expression analysis of SEQ ID NO 7, as well as

modifications, and variants of SEQ ID NO 7 and including any sequence of any modification, as broadly claimed, in different tissue and organ grafts to determine if in fact there was either an association between the expression of SEQ ID NO 7, modifications and homologues of SEQ ID NO 7 as well as any other sequence in a patient and graft reaction. The skilled artisan would have to perform an study of comparative expression analysis of SEQ ID NO 7 modifications and homologues of SEQ ID NO 7 as well as any other sequence in other species in other tissues to determine if SEQ ID NO 7 modifications and homologues of SEQ ID NO 7 as well as any other sequence is expressed comparatively in different tissues, organs, and species and then determine if this expression changes upon graft reaction. The results of such a study are unpredictable as evidence by the post filing art (which reflects the current state of the art) and the teachings in the specification. In the instant case, it would be unpredictable as to whether or not any expression level change of SEQ ID NO 7 modifications and homologues of SEQ ID NO 7 as well as any other sequence would be predictive of a graft reaction in a patient. In order to practice the invention as broadly as it is claimed, the skilled artisan would have to perform an extremely large amount of trial and error analysis in a large study to determine if such expression levels would predictably determine any or all graft reactions. Given the lack of guidance in the specification and the post filing art with respect to accurately testing genetic diseases, such analysis is replete with unpredictable experimentation and is considered undue.

Response to Arguments

8. The response traverses the rejection on pages 6-8 of the remarks mailed 06/05/2009. The response asserts that the specification describes a stably high expression in SEQ ID NO 7 is predictive of tolerance while a reduced SEQ ID NO 7 expression is predictive of graft rejection

and that one of skill in the art would recognize the detectable changes in the level of SEQ ID NO 7 are those changes that can be distinguished from a control level and thus the specification enables a person of ordinary skill in the art to practice the method. This response has been thoroughly reviewed but not found persuasive. The specification does not provide statistically significant data that predictably determines that a change in expression of SEQ ID NO 7 is predictive of graft reaction in any subject. The specification discloses an example in an animal model and does not provide statistically significant data for this model, much less provide analysis that this could and is predictive in humans. The specification does not provide any guidance that would allow the skilled artisan to detect SEQ ID NO 7, which is a rat cDNA in human nor provide any guidance as to what sequences are functional homologues of SEQ ID NO 7, nor provide any guidance as to what modification of SEQ ID NO 7 or any sequence, as broadly claimed that are predictive any graft reaction in any subject.

The response asserts that example 5 provides human homologues of sequences that have been identified. The response provides a sequence of a human homologue of SEQ ID NO 7 and asserts that it is routine for a person to identify homologous mRNA in related species and points to example 5 as describing sequence that exhibit regulation in human patients similar to animal models. This response has been thoroughly reviewed but not found persuasive. The examiner agrees that is it within the skill of the art to determine homologous mRNA sequences in related species, however the claims are not drawn to detecting homologous mRNA sequence the claims are drawn to detecting graft rejection by expression analysis of any nucleic acid sequence, homologues of any nucleic acid sequence, and modification of any nucleic acid sequences including SEQ ID NO 7. Thus the claims require the knowledge that expression of the nucleic

acid sequence is predictably associated with graft reaction in the subject. The specification does not provide any guidance to predictably determine the expression analysis of SEQ ID NO 7, or its modifications or homologues are predictably associated with any type of graft reaction in any species. Additionally, example 5 does not provide human homologues of SEQ ID NO 7, example 5 provides sequences for 1A50, 2A15, and 2A5. Additionally example 5 does not provide analysis of statistically significant expression of SEQ ID NO 7 or its homologues that would predictably detect any type of graft reaction in any other species.

The response asserts that the modified levels of SEQ ID NO 7 is used to detect graft reactions based on comparison against control levels and asserts that the difference in expression levels between control and toleration is used to determine rejection reaction over time not absolute level of expression. The examiner is not asserting that absolute level of expression is required for the claimed method, the examiner is asserting that the specification lacks guidance for the skilled artisan to determine the expression analysis of SEQ ID NO 7 to predictably determine a graft reaction in a sample. The specification does not provide statistically significant data of the expression analysis of SEQ ID NO 7, much less any homologue or modification of SEQ ID NO or any sequence in any species that would allow the skilled artisan to predictably determine a graft reaction in a sample.

The response asserts that figures 204 provide error bars of statistical analysis demonstrating that a number of animals were analyzed and a number of different transplants were determined. Additionally applicants asserts that data was found to be significant when $p < .05$ and submit a copy of these findings as published. This response has been thoroughly reviewed but not found persuasive. As stated in MPEP 2145 [R-2], Attorney argument is not

evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection. See MPEP § 2129 and § 2144.03 for a discussion of admissions as prior art. The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). See MPEP § 716.01(c) for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration. In the instant case, the attorney's argument that a number of animals were analyzed and a number of different transplants were determined, that data was found to be significant when $p < .05$ and submit a copy of these findings as published, were not presented in the specification and thus are not factual evidence and requires an appropriate affidavit or declaration to be of probative value which includes unexpected results and inoperability of the prior art. This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:

(1) prior to a final rejection,

(2) before appeal in an application not having a final rejection, *

(3) after final rejection **>, but before or on the same date of filing an appeal, upon a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented in compliance with 37 CFR 1.116(e); or

(4) after the prosecution is closed (e.g., after a final rejection, after appeal, or after allowance) if applicant files the affidavit or other evidence with a request for continued examination (RCE) under 37 CFR 1.114 in a utility or plant

application filed on or after June 8, 1995; or a continued prosecution application (CPA) under 37 CFR 1.53(d) in a design application.

For affidavits or declarations under 37 CFR 1.132 filed after appeal, see 37 CFR 41.33(d) and MPEP § 1206 and § 1211.03.

Additionally, it is noted that the claims are not limited to analysis of graft reaction in a rat by detecting an increased or decreased expression of SEQ ID NO 7 and this last response, as well as any evidence that would be provided would only be applicable to the analysis of graft reaction in an animal model with expression of SEQ ID NO 7, to which the claims are not limited.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 40-41, 43-45, 48 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Charpin (1998, cited on IDS).

Charpin et al. teach determining the level of mRNA in lung transplant receipts by competitive PCR (see pg. 753) (claim 41 and 44). Charpin et al. teaches graft reaction in patients with highest expression of TGF-β (see pg. 754), thus Charpin teaches increased expression in patients with graft reactions (claim 48). It is noted that claims do not require the detection of the sequence set forth in the sequence listing as SEQ ID NO 7 as the claims recite that "wherein

SEQ ID NO 7 is at least one nucleic acid molecule selected from the group consisting of (a) a nucleic acid molecule or its complementary nucleotide sequence" and therefore the claims merely require detecting a nucleic acid molecule, which is anticipated by Charpin.

Conclusion

11. No claims are allowable.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Sarae Bausch/
Primary Examiner, Art Unit 1634